65. The method according to claim 64 wherein said human subject is a man or post-menopausal woman.

C2 Cont 66. The method according to claim 64 wherein said osteoporosis is steroid-induced.

Remarks

Reconsideration of the application and entry of the foregoing amendments is respectfully requested. Applicants respectfully submit the amendments filed herewith obviate all bases of the rejection and place the application in condition for allowance.

Claims 17-34, and 36-55 have been cancelled without prejudice toward later claiming the subject matter contained therein.

Claim 35 has been amended to specify a method for treating osteoporosis and reducing the risk of bone fracture.

New claims 56-66 find support throughout the specification.

Claim 56 depends from claim 35 and specifies use of human PTH(1-34).

Claims 57-58 depend from claim 56 and specify a postmenopausal woman or a man, and osteoporosis that is steroid-induced. Support can be found, for example, at pages 6-7 and in Example 3 of the specification.

Claims 59 relates to the administration of parathyroid hormone once per week at a dose of 20 µg to 40 µg. Support for this claim can be found in the specification, at for example, page 13, line 12.

Claims 60-62 depend from claim 59 and specify, respectively, use of human PTH(1-34), a postmenopausal woman or a man, and osteoporosis that is steroid-induced. Support can be found, for example, at pages 6-7 and in Example 3 of the specification.

Claim 63 depends from claim 60 and specifies a dose of 20 ug.

Claims 64 depends from claim 56 and species a dose of 20 ug.

Claims 65-66 depend from claim 64.

Preliminary Amendment

The Office Action states that the amendment filed on September 26, 2000 to correct page 47, line 7 of the specification "could not be entered because 'µg/kg/day' does not appear in that line."

Applicants submit herewith an amendment to specify page 47, line 8. Applicants submit this amendment removes the basis for the rejection.

Inventorship Correction

Applicants' prior petition to correct inventorship under 37 CFR 1.48(b) was not accompanied by a statement from each person being added as an inventor that their omission as an inventor was an error that occurred without deceptive intention. Enclosed herewith is a statement to this effect, signed by each of the added inventors.

Background of the Invention

The present invention relates to the discovery that PTH can be administered to human subjects with osteoporosis to strengthen bone and reduce the risk of fracture in both vertebral and non-vertebral bone. The FDA recently granted Applicants approval to market PTH for use in the treatment of osteoporosis.

Differential Effect of PTH on Vertebral and Non-vertebral Bone

PTH is a hormone that stimulates bone building and bone resorption. The net effect on the skeleton of exogenously administered PTH depends in part on the dose regimen. When administered on a regular, intermittent basis, e.g. once daily, PTH increases bone mass. On the other hand, continuous administration produces net bone loss.

The bone-building property of PTH is itself variable and dependent on the particular site of action. For example, multiple studies have shown that exogenously administered PTH increases BMD of spinal bone while *decreasing* BMD of non-

vertebral (principally cortical) bone. This phenomenon of opposing effects on vertebral and nonvertebral bone has been termed "robbing Peter to pay Paul".[1]

As a means to mitigate the "robbing Peter" phenomenon, some investigators have taught combined therapeutic regimens, in which PTH is administered concomitantly with an anti-resorptive agent, or hormone replacement therapy ("HRT").

Applicants' Invention

Applicants' invention relates to the therapeutic use of PTH alone, without concomitant use of an anti-resorptive agent, or hormone replacement, for the treatment of osteoporosis. Applicants' large-scale clinical trial provided the first scientific evidence that PTH is safe and effective to treat osteoporosis, and to reduce the risk of fracture in vertebral and non-vertebral bone.

Applicants' discovery that exogenously administered PTH reduces the risk of bone fracture in osteoporosis patients is highly significant. While the prior art taught that exogenously administered PTH increases bone mineral density (BMD) in vertebral bone, there was no accepted correlation between increased BMD and reduction in the risk of bone fracture. Indeed, the art taught that compounds such as fluoride increased BMD while having no affect, or a negative affect, on the incidence of bone fracture.

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[1] The "robbing Peter to pay Paul" phenomenon is addressed in multiple references showing that intermittent PTH administration produces a decline in BMD, principally cortical bone. *See e.g.* Reeve et al. Brit. Med. J. 280, 1340 (1980); Hesp et al. Metab. Bone Dis. & Rel. Res., 2, 331 (1981); Reeve et al. E. J. Clin. Invest. 17, 421 (1987); Neer et al. Osteoporosis Int. Suppl. 1: S204 (1993); Riggs, Am. J. Med. 95, 5A-62S (1993); Whitfield and Morley, TIPS, 16, 382 (1995). Other references teach that PTH administration increases spinal BMD while producing no change in BMD in nonvertebral bone. *See e.g.* Neer et al. In *Osteoporosis 2*, Ed. Christiansen et al. 829 (1987); Slovik et al. J. Bone & Miner Res. 1, 377 (1986). Several review articles discuss this phenomenon further including, Dempster et al. Endocrine Rev, 14, 670, 701 (1993); Reginster et al. Osteoporosis Int. 7, Suppl. S163-168 (1997); and Hodsman et al. In *Parathyroid Hormone: The Clinical Experience & Prospects*, CRC Press, 83-108 (1998).

For example, Riggs states, "increased bone mass induced by treatment [i.e. with fluoride] does not necessarily correlate with increased bone strength . . . . Moreover . . . fluoride therapy significantly increased the rate of both incomplete and complete nonvertebral fracture." Riggs, *A. J. Med.* 91, 5B-39S.

In the same light, Hodsman states:

> The controversial studies of the use of sodium fluoride and bisphosphonates have not universally supported the assumption that increased bone mass . . . reduces fracture risk. **Nor are there definitive studies that indicate whether increases in bone mass induced by PTH will translate into a reduced fracture risk**. Hodsman et al. In *Parathyroid Hormone: the Clinical Experience & Prospects*, CRC Press 1998, pp 83-108 (emphasis added).

Thus, prior to Applicants' disclosure there was no teaching in the art, or suggestion, that an increase in BMD resulting from PTH treatment would reduce the risk of fracture.

Absence of an internationally recognized PTH standard

The utility of PTH as a therapeutic agent depends on administering an appropriate dose of PTH. Dosing regimens specify the mode of administration, the frequency of administration, and the amount or quantity of PTH that is administered. The amount of PTH can be designated as a weight amount of the peptide, or as units of activity. Since there is no recognized international standard for hPTH(1-34),[2]

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[2] Several PTH reference standards have been published, but none relate to human PTH(1-34). For example, a "first international reference preparation" for bovine PTH was established in 1974. A "first international reference preparation" for full length human PTH was established in 1981. The Extra Pharmacoepia, The pharmaceutical Press, London, 29th ed. 1989. It is well known in the art that species and fragment variations exist when assaying PTH activity, and when comparing the activity of full length PTH versus one of its active fragments, e.g. PTH(1-34). Fragment variations can be significant in in vivo assays, such as the chick hypercalcemic assay, owing to differences in peptide clearance rates. Additional variation in activity measurements are observed when comparing different assays.

specifying PTH dose as a weight amount is currently the most precise way to quantify the dosage of PTH(1-34).

PTH dose designations in units of activity have been fraught with ambiguity. "Units of activity" is a measure of the biological activity of a sample of PTH. Activity units are defined relative to the activity of a specified standard PTH preparation measured in an accepted assay for PTH activity.

The problems with specifying PTH(1-34) dose amounts in units of activity are substantial. As mentioned, one reason for this is that there is no internationally recognized standard for PTH(1-34) (*See* attached 1.132 declaration by Dr. Bruce Meiklejohn). As such, it is difficult, if not impossible, to correlate the amount of PTH in one sample to another sample short of doing side-by-side comparisons.

Many prior art references teach the administration of specified units of PTH activity to patients having osteoporosis. However, the dosages provided in these disclosures are quite ambiguous, not only for the reasons mentioned in the preceding paragraph, but also because in many instances there is failure to disclose *any* standard to calibrate units. Moreover, some references even fail to mention the assay used to measure activity. Such teachings are therefore decidedly ambiguous concerning the amount of PTH administered to a patient.

In other published references, PTH dosages are disclosed in terms of internal "house units" which relate to an "internal laboratory standard." Such internal standards provide no basis for reproduction by investigators outside the particular laboratory that disclosed it. Thus, a disclosure of "Y house units" of PTH activity cannot be accurately known or compared outside the laboratory that disclosed it.

A relevant problem in this respect is that experimental results may be difficult or impossible to reproduce from one laboratory to another. Only when a reference actually specifies the specific activity of the PTH used, or the units of activity along with a particular assay and reference standard, can there be confidence in quantifying the PTH dose.

Rejection Under 35 USC Section 112, Second Paragraph

Claims 17-55 were rejected allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants' regard as the invention. Specifically, claims 32, 34, 42-52, 54, and 55 were alleged to be indefinite in reciting the term "less than about," which "does not clearly define the lower limit of dosage of the parathyroid hormone."

Applicants have cancelled the rejected claims without conceding the basis for this rejection. Applicants reserve the right to later claim the subject matter embodied in the cancelled claims.

Applicants wish to respond to the rejection respecting newly added claims 56-65. The Examiner alleges indefiniteness based on lack of a clearly defined lower limit for the dosage of parathyroid hormone. The new claims specify a dose of 20 µg, or a range of 20 µg to 40 µg, per day or per week. Applicants assert the new claims render the rejection moot and request withdrawal of the rejection.

The rejection further asserts "Claims 17-55 are indefinite because the dosage of human parathyroid hormone is not defined clearly in the claims. Is a bolus administration intended? Is the amount related to the body weight of a patient?"

The requirement of Section 112, second paragraph, as stated by the Federal Circuit is: "whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, Section 112 demands no more . . . ." *Miles Laboratories, Inc. v. Shandon Inc.*, 27 USPQ2d 1123 (Fed. Cir. 1993).

Applicants respectfully traverse the assertion that the "dosage of hPTH is not defined clearly." The claims are directed at "administering" parathyroid hormone at a specified dosage amount and dosage frequency, which *would be* clearly understood by a skilled artisan. As such, Applicants

respectfully assert the claims fulfill the requirements of Section 112, second paragraph.

The rejection queries further, "Is a bolus administration intended?" Applicants respectfully assert this question has no bearing on the issue of indefiniteness. The claims are clear and definite without addressing whether a bolus administration, or any other kind of administration, is intended. The specification makes clear that a variety of dosage regimens are contemplated including parenteral and subcutaneous injection, administered regularly (e.g. once or more per day, or week). Moreover, the claims clearly specify a dosage amount of parathyroid hormone. With due respect, the particular mode of administration is unnecessary to the clarity of the claim.

This basis of the rejection suggests concern with the breadth of the claims. However, Federal Circuit case law holds that "mere breadth of a claim is not indefiniteness if it is understandable." *Aptargroup, Inc. v. Summit Packaging Systems*, 1998 U.S. App. LEXIS 28047 (Fed. Cir. 1998). Applicants' claims cannot be said to be indefinite when viewed by a skilled artisan. Applicants are entitled to claim their invention as broadly as the prior art, and the support of the specification will allow.

The Examiner further asks, "Is the amount related to the body weight of a patient?" Applicants claim the administration of a specified amount of PTH without regard to the bodyweight of the patient (cf. Example 3). Applicants respectfully submit there is no indefiniteness problem with the claimed dosage and that the claims would be clearly understood by a skilled man, thereby fulfilling the requirement of Section 112, second paragraph.

Applicants respectfully request withdrawal of this basis of the rejection, and passage of the case to issuance as soon as possible.

Rejection Under 35 U.S.C. Section 102

Rejection over Sone et al.

Claims 17-52, 54, and 55 were rejected, allegedly as being anticipated by Sone et al. (hereinafter "Sone"). Sone teaches the administration of PTH(1-34) at 6 μg per day for 26 weeks to treat osteoporosis patients. Sone showed an increase of bone mineral density (BMD) in spinal bone. Sone does not teach a reduction in the risk of fracture.

Anticipation arises when a single reference discloses, explicitly or inherently, each and every claim limitation. Sone teaches the administration of 6 ug/day of PTH(1-34) to treat osteoporosis. Applicants' claimed dosage differs from Sone's dosage. Applicants' lowest dosage is 20 μg/day. In contrast, Sone teaches a dose of 6 μg/day. Thus, there is no anticipation by Sone. Applicants respectfully request withdrawal of this basis of the rejection.

The Examiner states, "The increase in bone mass and BMD reduces the risk of fracture of vertebral bone and non-vertebral bone, trabecular and cortical bone." While Applicants traverse the relevance of this statement to the issue of anticipation they nonetheless offer the following comments in rebuttal.

Prior to Applicants' disclosure there was no correlation in the art between increased BMD on the administration of PTH and reduction in the risk of fracture. In fact, as noted previously, the prior art provides examples of other bone mineralization agents that prove the contrary, namely that an increase in BMD does not correlate with a reduction in bone fracture. For example, fluoride treatment results in an increase in bone mass, but does not reduce the risk of fracture. (See Hodsman et al. "Parathyroid Hormone: The clinical experience and prospects." Chap. 4, p.89, (1998); Riggs, A. J. Med. 91, 5B-39S). Thus, there was no evidence in the prior art, prior to Applicants' disclosure, that administration of PTH would reduce the risk of fracture.

The Examiner further states, "It should be noted that the dosage of the PTH is not defined unambiguously in the claims and that the amount (μg) of a PTH is [sic] depends upon the purity, activity, and size of the hormone or its active fragments." Applicants respectfully traverse the relevancy of this statement to the issue of anticipation.

Applicants' claim unambiguous quantities of the therapeutic agent PTH for the treatment of osteoporosis and reduction in the risk of bone fracture. Thousands of issued United States Patents claim therapeutic regimens in terms of administration of specified ug quantities of a drug agent. Thus, Applicants fail to understand the basis for the Examiner's statement. Applicants' claimed dosage is not limited to the purity, activity, or size of the hormone.

The Examiner further asserts, "the specific details listed in the preambles are not accorded patentable weight (e.g. the specific bone parts listed in claim 36). Without conceding this basis of the rejection, Applicants have cancelled the relevant claims without prejudice to later claiming the subject matter contained therein.

The Examiner further asserts, "A packaging material comprising a printed matter insert (see claim 27) does not constitute a patentable subject matter." Without prejudice Applicants have cancelled claim 27 while reserving the right to later claims this subject matter.

Applicants submit their claims are novel over Sone, and respectfully request withdrawal of this basis of the rejection.

Rejection Over Neer et al.

Claims 17, 19, 21, 23, 25-28, 30, 32-36, 38-40, 42, 43, 45-47, and 49-55 were rejected, allegedly as being anticipated by Neer et al. (hereinafter "Neer"). Neer teaches the use of PTH, including PTH(1-34), to increase bone mass in an osteoporosis patient. Neer discloses dose ranges of "100-700 units/day, more preferably 200-600 units/day, and most preferably 400-500 units/day, wherein units are defined in terms of the International Reference Preparation of hPTHF 1-34

and comparative bioassays in one of the established PTH bioassays." (Col. 5, lines 1-8). Neer further teaches that "units" are expressed in the chick hypercalcemic assay. Neer does not teach dose amounts of PTH as a weight quantity, nor does Neer teach the specific activity of PTH(1-34).

The Examiner asserts, without citation to authority, that a known conversion relationship exists between specific activity and mass quantities of PTH. Specifically, "Based upon the calculation that 400 units = 25 µg, 100-700 units/day is equivalent to 6.3-43.8 µg/day whereas 400-500 units/day is equivalent to 25-31 µg/day." Applicants respectfully challenge the basis for this position.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (citing *Verdegaal Bros. V. Union Oil Co.*, 2 USPQ2d 1051 (Fed. Cir. 1987).

I. Neer fails to anticipate the claimed invention

Neer fails to *expressly* disclose the claimed microgram dosage of PTH, and as such does not anticipate. Neer teaches dosages that are expressed in Units of activity. As any skilled artisan knows, there is no basis to correlate units of activity with a corresponding weight amount unless the specific activity is known, disclosed, or can be derived. Here, Neer not only fails to teach the specific activity of PTH(1-34), but *also fails to enable its determination*. Thus, Neer does not expressly teach, nor enable, the determination of the weight amount for PTH(1-34) corresponding to Neer's disclosed Units dosage.

Notwithstanding the absence of an explicit disclosure respecting the microgram quantity of Neer's dosage, the Examiner nonetheless asserts that the dosage of Neer can be converted from units to micrograms by *importing* a specific activity (presumably from the prior art), and applying the imported value to Neer. Specifically, the Examiner imports a specific activity that 400 units is equivalent to 25 ug, (i.e.

16 Units/ug). Applicants respectfully traverse the legal and technical grounds for this action.

First, it is contrary to established case law to supplement an alleged anticipatory reference with information not contained in that reference. *In re Marshall*, 198 USPQ 344 (CCPA 1970). A limited exception allows supplementation with extrinsic evidence, but only "when it is used to explain, but not to expand the meaning of a reference." *In re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed. Cir. 1991). Thus, missing elements from an alleged anticipatory reference may not be supplied by the knowledge of a skilled artisan, or the disclosure of another reference. Applicants respectfully assert the alleged anticipation over Neer is based on an impermissible importation of specific activity information not contained in Neer. Applicants respectfully request withdrawal of this basis of the rejection.

Neer fails to anticipate under inherency

A reference that does not explicitly disclose a claimed element may anticipate *if* such a disclosure is inherent. However, inherency requires: 1) the missing descriptive matter must *necessarily* be present in the reference, (emphasis added) *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999); and 2) the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows form the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990)(MPEP §2112).

Here, there is no basis in Neer, or any other cited art, for the specific activity selected by the Examiner, namely 16 U/ug. While Applicants concede the *possibility* that Neer's PTH had a specific activity of 16 U/ug, this is unknowable under the circumstances and very far from certainty. As such, this cannot serve as a basis for alleging anticipation by inherency.

Furthermore, there is no *certainty* that Neer's actual specific activity even falls within the range of values

taught in the prior art. A survey of the prior art reveals that PTH(1-34) specific activity values vary significantly from laboratory to laboratory, and from lot to lot within a given laboratory, going from 3 Units/ug to 16 Units/ug.[3] Statistical analysis of the data set of specific activity values from the prior art shows a 5%-10% possibility that Neer would fall *outside* the range of values disclosed in the art (*See* Appendix).

Thus, there is no *certainty* in assigning a specific activity value to Neer, and as such, no basis for an inherency argument for anticipation.

II. Neer fails to meet the legal requirements for an anticipatory reference

It is axiomatic under the law of anticipation that a reference *must be enabled in order to anticipate*. "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' . . . within section 102, the stated test is whether a reference contains an 'enabling disclosure' . . . . *In re Hoeksema*, 158 USPQ 596 (CCPA 1968)(MPEP §2121.01). In evaluating enablement, the courts have found enablement when "one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention." *In re Donohue*, 226 USPQ 619 (Fed. Cir. 1985).

Applicants assert Neer fails to enable the determination of the specific activity for PTH(1-34). As such, Neer fails to fulfill the requirements of an anticipatory reference. Applicants therefore respectfully request removal of this reference as a basis of rejection.

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[3] Sone teaches a specific activity for PTH(1-34) at 3 U/ug (Miner Electrolyte Metab. 21, 232-235 (1995); Lindsay et al. teach a specific activity for PTH(1-34) at 16 U/ug (Lancet, 350, 550-555 (1997); Lane et al teach a specific activity for PTH(1-34) at 16 U/ug (J. Clin Invest. 102, 1627 (1998); Finkelstein et al teach a specific activity for PTH(1-34) at 12.5 U/ug (JAMA, 280, 1067 (1998); Hodsman et al. teach a specific activity for PTH(1-34) at 15 U/ug (J. Clin. Endo. Metab. 82,620 (1997); Reeve et al. teach a specific activity range for PTH(1-34) from 5 U/ug- 7.5 U/ug (Brit Med J. 280, 1340 (1980); Reeve et al. teach a specific activity for PTH(1-34) at 10 "house units"/ug (E. J. Clin. Invest. 17,421 (1987).

Neer states unambiguously that units of activity of PTH(1-34) were measured in the chick hypercalcemic assay (Col 5), and that "units are defined in terms of the International Reference Preparation of hPTHF 1-34" (Col 5). Thus, Neer stipulates the procedure that is to be followed in determining the specific activity value of PTH(1-34), and for converting units to micrograms of PTH(1-34).

While Neer stipulates a specific assay procedure for measuring activity, that procedure *cannot* be performed, because, as stated in the accompanying 1.132 declaration by Dr. Meiklejohn, the reference standard specified by Neer does not exist.

The significance of this finding cannot be overstated. *Arguendo*, assume one were interested in comparing the units of PTH(1-34) in hypothetical sample *X* against Neer's units dose. In order to make such a comparison one would need to follow the procedure stipulated by Neer. Otherwise the comparison would be meaningless, like comparing apples and oranges. Neer stipulates that the determination of units of PTH activity is based on the chick hypercalcemic assay, against the "International Reference Preparation of hPTHF 1-34." In order to unambiguously compare the units of activity in Sample X with Neer's units dosage, one would need to determine the activity of Sample *X* in the chick hypercalcemic assay, against the "International Standard" stipulated by Neer. This cannot be done. As supported by the attached Meiklejohn declaration, Applicants are unaware that such a standard exists. As such, there is no credible basis for comparing Neer with other references, or samples of PTH(1-34). Under these circumstances, Neer should be regarded as an island unto itself providing no basis for alleged anticipation.

The variability in PTH activity measurements and the indispensability of a reference standard is well known to the skilled artisan. As supported in the attached 1.132 declaration by Dr. Griffiths, specific activity measurements for PTH are in fact highly sensitive to the particular assay used and the standard used for calibration. The skilled

artisan well appreciates the vagaries in trying to measure and compare PTH activities. For example:

> The biologic activity of hPTH(1-34) per unit weight seems to differ between studies. In Lindsay et al.'s study (Lancet 1997; 350:550-5) . . . 400 U (25 µg) of hPTH(1-34) was used. . . . *[I]t is **difficult to compare the results** of the present study with those of others with reference to the doses of hPTH(1-34) because of differences in the preparation used* . . . . *Id.* at 303. (emphasis added).

Further variations in the activity of PTH are well documented when comparing PTH molecules from different species, even using the same assay, or when comparing the same PTH molecule in different assays.[4] There is also significant variation when comparing full length PTH to one of its fragments, *e.g.* PTH(1-34).

In summary, without access to the reference standard stipulated by Neer there is no way to unambiguously compare Neer's units dosage to other dosage disclosures, whether comparing units or micrograms. Applicants respectfully assert Neer fails to anticipate the claimed invention, and respectfully request withdrawal of this basis of the rejection.

Summary respecting Neer

Neer fails to anticipate the claimed invention, for the following reasons:

- Neer fails to disclose the claimed invention, either expressly or inherently.
- Neer fails to qualify as an anticipatory reference since it is non-enabled.

Claims 63-66

While Applicants traverse the alleged anticipation

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[4] For example, Parsons et al. showed between a 3 and 10-fold difference in comparing the same PTH molecule in different assays. Furthermore, the activity of different PTH molecules in the same assay showed a dramatic difference in activity of some 2 to 40-fold. *See* Parsons et al. In Calcium-regulating hormones. Proceedings of the Fifth Parathyroid Conference Oxford, UK July 21-26, pp 33-40; 1974; Ed R. Talmage et al. American Elsevier Publ. Co. (1975).

rejection as applied to *all* the claims, for the reasons presented herein, claims 63-66 deserve special comment. Claims 63-66 are limited to a dose of 20 ug. Notwithstanding Applicants' vigorous objection, on legal and technical grounds, to the importation of a specific activity from the prior art to interpret Neer, Applicants note that whatever specific activity is applied to Neer, these claims are novel. For example, *assuming* a value from the prior art of 3 U/ug, (the value disclosed by Sone et al.), Neer's units dosage range would convert to 33 ug to 233 ug/day, clearly outside the dose specified in these claims.

Applicants respectfully submit the rejection has been overcome and request the Examiner to withdraw the rejection and advance the case to issuance without further delay.

Respectfully submitted,

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APPENDIX

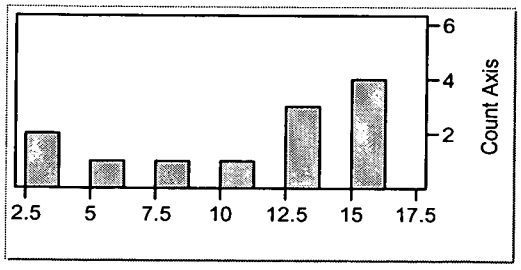
Statistical Analysis of Published Specific Activity Values for PTH(1-34)

A sampling of specific activity values for PTH(1-34) taken from the cited art are displayed in the Table. The values range from 3 U/ug to 16 U/ug.

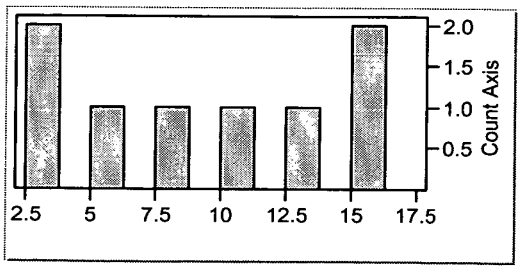
Reference	IDS Reference Code	Specific Activity (units/ug)
Finkelstein (1994)	CAH	12.5
Finkelstein (1998)	CAG	12.5
Finkelstein (1999)	CAE	12.5
Fujita (1999)	CL	3.3
Hodsman (1997)	CN	15
Lane (1998)	CE	16
Lindsay (1997)	CB	16
Lindsay (1993)	CD	16
Reeve (1980)	CO	5
Reeve (1980)	CO	7.5
Reeve (1987)	CU	10
Sone (1995)	CAA	3

The specific activity data are plotted on a histogram below, either using all 12 values from the Table, or using only the 8 unique values to reflect the possibility of replicate values from the same laboratory.

Histogram of all 12 values



Histogram of the 8 unique values



The evidence is not sufficient under the Shapiro-Wilk W test to rule out a normal distribution as a model for these data. On the assumption of a normal distribution, the probability that an individual lab, picked at random, could produce a specific activity less than 2.5 Units/mg is 0.05 (5%) using all 12 values, or 0.10 (10%) using the 8 unique values.

If one does not assume a normal distribution, percentiles can be computed directly from the data. Using the calculation of percentiles that is defined in the JMP software (SAS Institute), the smallest value from a set of N values, is the *P*-th percentile, where,

$P = 100 / (N+1)$

Thus, the smallest value from the data set in the Table, 3 U/ug, is the 11-th percentile (100/9=11.1) in the set of 8 unique values above. This means that the probability that a randomly sampled laboratory could produce a value less than 3 is 11%.

This latter result is consistent with the result assuming a normal theory.

The probability, *p*, is calculated using either the standard normal distribution or Student's t distribution with the following formula:

$p = F [(2.5 - m) / s]$

where F is the distribution function, *m* is the sample mean, and *s* is the sample standard deviation.

Version of Amended Claims Showing Changes Made

35. A method for the treatment of osteoporosis [reducing the risk of vertebral and non-vertebral bone fracture] in a human subject [having osteoporosis], comprising administering to said subject a parathyroid hormone, without concurrent administration of an antiresorptive agent other than vitamin D or calcium, in a daily dose of 20 µg to 40 µg said treatment for reducing the risk of vertebral and non-vertebral bone fracture.